

# ASSOCIATION BETWEEN VITAMIN D LEVELS AND TRANSIENT POSTOPERATIVE HYPOCALCEMIA IN THYROIDECTOMY

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## ARTICLE INFO

### Keywords:

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## ABSTRACT

Transient postoperative hypocalcemia (TPH) is the most common complication after thyroidectomy. Several studies have suggested that vitamin D deficiency may play a role in its occurrence, although available evidence remains inconsistent. The objective was to evaluate the association between serum vitamin D levels and the occurrence of TPH in patients undergoing total thyroidectomy for thyroid disease. **Materials and methods:** An observational, analytical, and retrospective study was conducted in patients over 18 years of age who underwent surgery at Hospital Dr. Arturo Oñativia during 2022 and 2023. Patients with diseases or treatments that could alter calcium-phosphate metabolism were excluded. TPH was defined as serum calcium <8.5 mg/dL during the first two postoperative days. Vitamin D [25(OH)D] levels were classified as sufficient ( $\geq 30$  ng/mL), insufficient (20-29 ng/mL), deficient (<20 ng/mL), or severely deficient (<10 ng/mL). **Results:** Ninety-seven patients were analyzed, with a median age of 53 years; 85.6% were women. Pathology was benign in 60.8% and malignant in 39.2%. Total thyroidectomy was performed in 77.3% and thyroidectomy with neck dissection in 22.7%. The overall incidence of TPH was 59.6%. Regarding 25(OH)D, 10.3% had sufficient levels, 34% insufficient, 47.4% deficient, and 8.2% severely deficient. No significant association was found between 25(OH)D levels and the occurrence of TPH. The type of surgery was significantly associated with TPH (OR 5.54; 95% CI 1.52-18.65;  $p < 0.006$ ). **Conclusion:** In this cohort, vitamin D deficiency was not associated with the occurrence of transient postoperative hypocalcemia.

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## ASOCIACIÓN ENTRE LOS NIVELES DE VITAMINA D Y LA HIPOCALCEMIA POSOPERATORIA TRANSITORIA EN TIROIDECTOMÍA

### INFO ARTÍCULO

#### Palabras clave:

hipocalcemia posoperatoria, hipoparatiroidismo, vitamina D, hormona paratiroidea, tiroidectomía.

### RESUMEN

La hipocalcemia posoperatoria transitoria (HPT) constituye la complicación más frecuente tras la tiroidectomía. Diversos estudios han sugerido que la deficiencia de vitamina D podría influir en su aparición, aunque la evidencia disponible resulta contradictoria. El objetivo fue evaluar la asociación entre los niveles séricos de vitamina D y la aparición de HPT en pacientes sometidos a tiroidectomía total por patología tiroidea. Materiales y métodos: se realizó un estudio observacional, analítico y retrospectivo en pacientes mayores de 18 años intervenidos quirúrgicamente en el Hospital Dr. Arturo Oñativía (Salta, Argentina) durante 2022 y 2023. Se excluyeron aquellos con enfermedades o tratamientos que modificaran el metabolismo fosfocálcico. Se definió HPT como una calcemia sérica  $<8,5$  mg/dL en los dos primeros días posoperatorios. Los niveles de vitamina D [25(OH)D] se clasificaron como suficiencia ( $\geq 30$  ng/mL), insuficiencia (20-29 ng/mL), deficiencia ( $<20$  ng/mL) y deficiencia severa ( $<10$  ng/mL). Resultados: se analizaron 97 pacientes, con una mediana de edad de 53 años; el 85,6% fueron mujeres. La patología fue benigna en el 60,8% y maligna en el 39,2%. El 77,3% fue sometido a tiroidectomía total y el 22,7% a tiroidectomía con vaciamiento. La incidencia global de HPT fue del 59,6%. El 10,3% presentó suficiencia de 25(OH)D, 34% insuficiencia, 47,4% deficiencia y 8,2% deficiencia severa. No se hallaron diferencias significativas entre los niveles 25(OH)D y la frecuencia de HPT. El tipo de cirugía sí mostró asociación significativa con HPT (OR 5,54; IC 95%: 1,5-18,6;  $p < 0,006$ ). Conclusión: en esta cohorte, la deficiencia de vitamina D no se asoció con la aparición de hipocalcemia transitoria posoperatoria.

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### INTRODUCTION

Transient postoperative hypocalcemia (TPH) is the most common complication following total thyroidectomy and may be associated with increased morbidity and, in severe cases, mortality [1-3]. Reported incidence varies widely, from 1.6% to 50%, making it difficult to establish precise figures [1,4]. TPH often prolongs hospitalization and recovery time, requires additional biochemical testing, and is associated with higher healthcare costs and morbidity burden [1,5-7].

The pathophysiology of this complication

is multifactorial and includes direct injury to the parathyroid glands, impairment of their vascular supply, or inadvertent resection, which may lead to transient or permanent hypoparathyroidism [1,3,8]. In this context, vitamin D plays an essential role in calcium homeostasis by promoting intestinal calcium absorption and modulating calcitriol synthesis in response to parathyroid hormone (PTH) [2,8-10]. Adequate preoperative vitamin D status may mitigate postoperative declines in serum calcium levels, whereas deficiency has been linked to a higher risk of

hypocalcemia [1,6,8,11,12]. Consequently, preoperative vitamin D levels have been proposed to influence calcium kinetics and act as a risk factor for postoperative hypocalcemia [6,13].

However, other studies have found no significant association between the two variables [14,15]. These discrepancies may be attributed to differences in hypocalcemia definitions, the thresholds used to classify vitamin D levels, and the heterogeneity of the study populations.

Given that vitamin D deficiency is a widespread public health issue in the general population, it is pertinent to clarify its role as a predictor of postoperative hypocalcemia. The aim of the present study was to evaluate the association between preoperative vitamin D levels and the occurrence of transient postoperative hypocalcemia in patients undergoing total thyroidectomy at Dr. Arturo Oñativia Hospital, Salta, Argentina.

## MATERIALS AND METHODS

A retrospective, observational, and analytical study was conducted. Patients who underwent total thyroidectomy for benign or malignant thyroid disease at Dr. Arturo Oñativia Hospital (Salta, Argentina), within the Endocrinology Program, between January 2022 and December 2023 were included.

### Inclusion criteria

1. Patients older than 18 years.
2. Total thyroidectomy performed for benign or malignant thyroid disease.
3. Availability of the final histopathological report.
4. Serum 25-hydroxyvitamin D [25(OH)D] measurement performed within 30 days prior to surgery.

### Exclusion criteria

1. Accidental parathyroidectomy confirmed in the histopathological report.
2. Conditions that alter phosphocalcic metabolism (Paget's disease, hyperparathyroidism, chronic kidney disease, among others).

3. Treatment with lithium or thiazide diuretics.
4. Ongoing treatment for osteoporosis.
5. Preoperative supplementation with calcium and/or vitamin D.

## Variables and data collection

Demographic, clinical, and biochemical variables were recorded, including serum levels of 25(OH)D, calcium, and albumin. Patients were classified according to 25(OH)D levels into four categories:

- Severe deficiency: <10 ng/mL
- Deficiency: <20 ng/mL
- Insufficiency: 20-29 ng/mL
- Sufficiency: ≥30 ng/mL

The type of surgery was categorized as follows:

- Bilateral total thyroidectomy (BTT): complete removal of thyroid tissue without associated lymph node dissection.
- Bilateral total thyroidectomy with lymph node dissection (BTT+LND): total thyroidectomy with concurrent central and/or lateral lymph node dissection.

## Primary outcome

The primary outcome was the occurrence of postoperative hypocalcemia, defined as:

- *Biochemical hypocalcemia*: any serum calcium value corrected for albumin <8.5 mg/dL, using the formula: *Corrected calcium* = serum calcium + 0.8 × (4.0 – serum albumin).
- *Symptomatic hypocalcemia*: presence of symptoms or clinical signs consistent with hypocalcemia (tingling, paresthesias, or carpopedal spasm) associated with biochemical hypocalcemia.

## Statistical analysis

Qualitative variables were expressed as absolute and relative frequencies (%), and quantitative variables as mean±standard deviation (SD) or median and interquartile range (IQR), depending on their distribution.

The association between postoperative hypocalcemia and categorical variables (sex,

thyroid function, type of surgery, histology, and vitamin D categories) was evaluated using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using Student's t test or the Mann-Whitney U test, according to the normality of the distribution, which was assessed with the Shapiro-Wilk test.

Odds ratios (OR) with their corresponding 95% confidence intervals (95% CI) were calculated to estimate the strength of the association between vitamin D levels, type of surgery, and the presence of postoperative hypocalcemia.

A p value <0.05 was considered statistically significant.

#### *Ethical considerations*

The study was approved by the Teaching and Research Committee of Dr. Arturo Oñativia Hospital, following presentation of the study objectives and protocol. Data collection and analysis were carried out ensuring confidentiality and anonymity of the information obtained, in accordance with ethical principles for clinical research.

## RESULTS

A total of 97 patients who underwent total thyroidectomy were included. Among them, 8 (8.2%) had severe vitamin D deficiency, 46 (47.4%) deficiency, 33 (34.0%) insufficiency, and 10 (10.3%) sufficiency.

The demographic and clinical characteristics of the population are summarized in Table 1. Most patients were women (85.6%), with a median age of 53 years (interquartile range 25-75). Regarding preoperative thyroid function, 54.6% were euthyroid, 23.7% had hyperthyroidism, and 21.6% hypothyroidism.

With respect to the type of surgery, 77.3% underwent BTT and 22.7% BTT+LND. Final histopathological analysis showed benign disease in 60.8% and malignant disease in 39.2% of cases.

The mean preoperative serum calcium level was  $9.24 \pm 0.42$  mg/dL (range 8.5-11.0). The overall incidence of transient postoperative hypocalcemia was 59.6%.

When comparing the baseline characteristics of patients with and without transient postoperative hypocalcemia,

**Table 1.** Population and clinical characteristics of patients undergoing surgery for thyroid disease. Notes: mean $\pm$ SD for normally distributed variables; median and IQR (25–75) for non-normally distributed variables.

Characteristics	Patients (n=97)
<b>Female sex, n (%)</b>	83 (85.6)
<b>Age, years, median (IQR)</b>	53 (39-67)
<b>Thyroid function, n (%)</b>	
Euthyroid	53 (54.6)
Hyperthyroidism	23 (23.7)
Hypothyroidism	21 (21.6)
<b>Type of surgery, n (%)</b>	
BTT	75 (77.3)
BTT+LND	22 (22.7)
<b>Final histology, n (%)</b>	
Benign	59 (60.8)
Malignant	38 (39.2)
<b>Preoperative calcium, mean (SD)</b>	9.24 (8.51-10.4)
<b>TPH, n (%)</b>	58 (59.6)

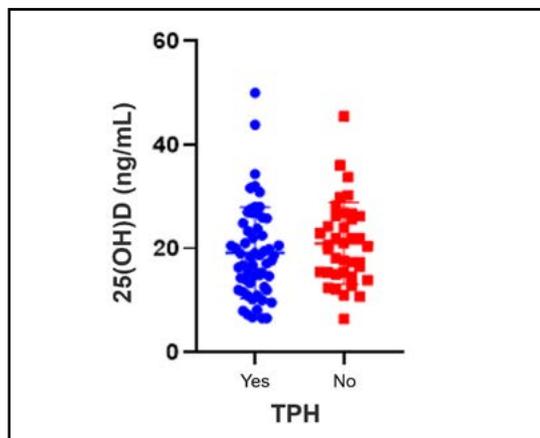
*Abbreviations:* BTT, bilateral total thyroidectomy; BTT+LND, bilateral total thyroidectomy with lymph node dissection; TPH, transient postoperative hypocalcemia.

no significant differences were observed in preoperative calcium levels or in the distribution of benign versus malignant pathology. The presence of hyperthyroidism was significantly associated with a higher frequency of hypocalcemia ( $p=0.005$ ). The type of surgery was a determining factor: patients who underwent BTT+LND showed a higher incidence of hypocalcemia compared with those who underwent BTT ( $p<0.006$ ) (Table 2).

When analyzing the association between 25(OH)D levels and the occurrence of postoperative hypocalcemia, no statistically significant differences were found among the groups ( $p=0.25$ ) (Figure 1). In the group with sufficient 25(OH)D levels, 60.0% developed hypocalcemia; 51.5% among those with insufficiency; 63.0% among those with deficiency; and 85.7% among those with severe deficiency (Table 3).

Among patients who underwent BTT, 40% presented hypocalcemia, whereas in those who underwent BTT+LND, the frequency increased

to 79%. This association was statistically significant ( $p<0.006$ ) (Pearson's  $\chi^2$ ) (Figure 2).



**Figure 1.** Serum 25(OH)D levels according to the presence of transient postoperative hypocalcemia. Serum 25(OH)D values (ng/mL) were compared between patients with (TPH Yes) and without transient postoperative hypocalcemia (TPH No). No statistically significant differences were observed between the two groups ( $p=0.25$ , Mann–Whitney U test).

**Table 2.** Comparison of baseline characteristics according to the presence of postoperative hypocalcemia.

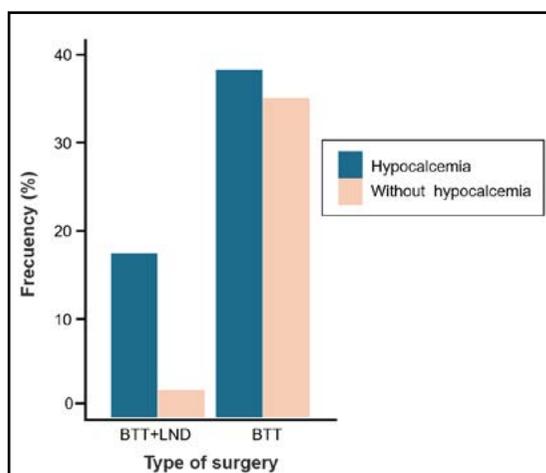
Baseline characteristics	With postoperative hypocalcemia (n=59)	Without postoperative hypocalcemia (n=38)	p
Preoperative calcium, mg/dL, median (IQR)	9.19 (8.51-10.1)	9.32 (8.58-10.4)	0.089 *
<b>Thyroid function, n (%)</b>			
Euthyroid	28 (47.5)	25 (65.8)	0.07 **
Hyperthyroidism	20 (33.9)	3 (7.9)	0.005 ***
Hypothyroidism	11 (18.6)	10 (26.3)	0.37 **
<b>Type of surgery, n (%)</b>			
BTT	40 (67.8)	35 (92.1)	<0.006 ***
BTT+LND	19 (32.2)	3 (7.9)	
<b>Final histology, n (%)</b>			
Benign	34 (57.6)	25 (65.8)	0.383 **
Malignant	25 (42.4)	13 (34.2)	

Notes: \*Student's t test; \*\*Pearson's  $\chi^2$  test; \*\*Fisher's exact test. LND, lymph node dissection; IQR, interquartile range. Abbreviations: BTT, bilateral total thyroidectomy; BTT+LND, bilateral total thyroidectomy with lymph node dissection; IQR, interquartile range.

**Table 3.** Association between vitamin D levels and the presence of transient postoperative hypocalcemia.

Vitamin D categories (ng/mL)	n (%)	With hypocalcemia, n (%)	Without hypocalcemia, n (%)
Severe deficiency (<10)	8 (8.2)	7 (85.7)	1 (14.3)
Deficiency (<20)	46 (47.4)	29 (63.0)	17 (37.0)
Insufficiency (20-29)	33 (34.0)	17 (51.5)	16 (48.5)
Sufficiency (≥30)	10 (10.3)	6 (60.0)	4 (40.0)
<b>Total</b>	<b>97 (100)</b>	<b>59 (59.6)</b>	<b>38 (40.4)</b>

Note:  $p=0.25$  (Pearson's  $\chi^2$  test).



**Figure 2.** Association between hypocalcemia and type of surgery. Percentage distribution of postoperative hypocalcemia according to the type of procedure: bilateral total thyroidectomy (BTT) versus bilateral total thyroidectomy with lymph node dissection (BTT+LND). A higher proportion of hypocalcemia is observed in patients who underwent BTT+LND.

*Abbreviations:* BTT, bilateral total thyroidectomy; LND, cervical lymph node dissection.

In the logistic regression analysis, BTT+LND was significantly associated with the occurrence of postoperative hypocalcemia, with an OR of 5.54 (95% CI: 1.52-18.65;  $p<0.006$ ).

## DISCUSSION

In our cohort, the incidence of transient postoperative hypocalcemia (59.6%) was within

the upper range of that reported in the literature (1.6-50%) and was comparable to local series [1,2]. Moreover, no significant association was observed between serum vitamin D levels and the occurrence of hypocalcemia, whereas the extent of surgery—particularly BTT+LND—emerged as the main associated factor.

Vitamin D plays a crucial role in the regulation of calcium and PTH, and its preoperative levels could theoretically influence recovery following total thyroidectomy. Although vitamin D deficiency may induce compensatory parathyroid hyperplasia, it may also increase susceptibility to postoperative hypocalcemia. In this study, preoperative vitamin D levels were not found to be predictors of hypocalcemia, a result consistent with that reported by Griffin et al. [16]. The analysis showed that serum 25(OH)D levels were not significantly associated with the development of postoperative hypocalcemia, even when considering different degrees of deficiency.

This finding contrasts with several studies that have reported an association between hypovitaminosis D and an increased risk of post-thyroidectomy hypocalcemia [2,5,6, 11,17]. In those reports, both deficiency and insufficiency of 25(OH)D were described as predictors of the outcome, although considerable heterogeneity existed in the cut-off values used and in the diagnostic criteria for hypocalcemia. Conversely, other authors agree with our findings, reporting no significant

relationship [16,19,20], underscoring the lack of consensus and the need for prospective studies with homogeneous criteria and larger samples. Furthermore, although no significant effect of vitamin D levels on the incidence of hypocalcemia was observed, the small number of patients with sufficient levels limits the ability to rule out subtle differences in postoperative calcium between groups. These discrepancies regarding the role of vitamin D may be attributed to multiple factors, including differences in sample size, the baseline prevalence of hypovitaminosis D across populations, the variability in cut-off values used to define sufficiency, and the lack of uniformity in the diagnostic criteria for postoperative hypocalcemia [8,9,21]. In this regard, future studies should consider a prospective design evaluating not only serum 25(OH)D levels but also the dynamic variations of PTH and calcium during the early postoperative period.

In our analysis, the type of surgery was the factor that showed a significant association with postoperative hypocalcemia, particularly BTT+LND. This finding is consistent with what has been reported in the literature, where the extent of the procedure and manipulation of the parathyroid glands are recognized as the main determinants of hypocalcemia risk [1,2]. Likewise, a history of hyperthyroidism was significantly associated with the occurrence of hypocalcemia, in agreement with international series that describe it as a predisposing factor, likely related to increased bone turnover and preexisting alterations in calcium homeostasis [22,23].

Among the strengths of this study is the analysis of a contemporary cohort of patients treated at a referral hospital, with a detailed stratification of vitamin D levels into

four categories. However, the retrospective design and sample size may have limited the statistical power to detect subtle associations, particularly in the extreme vitamin D categories. An additional limitation was that preoperative 25(OH)D measurements were available for only 24% of the patients, among whom a high prevalence of hypovitaminosis D was observed: 34.2% with insufficiency, 47.4% with deficiency, and only 10% with sufficient levels.

In conclusion, in this cohort of patients undergoing total thyroidectomy, transient postoperative hypocalcemia was confirmed as a frequent complication. No significant association was found between preoperative vitamin D levels and the occurrence of postoperative hypocalcemia, in contrast to several international studies. The factor most strongly associated with hypocalcemia was surgical extent, particularly BTT+LND, together with a history of hyperthyroidism, likely related to the institution's referral profile. These findings reinforce the importance of close clinical and biochemical monitoring in the immediate postoperative period, especially in patients undergoing more extensive procedures or those with more complex thyroid disease.

#### **Conflicts of interest**

The authors declare no conflicts of interest.

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#### **Author contributions**

All authors participated in the conception of the study, drafted the manuscript, and critically revised its content. All authors approved the final version.

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